SYSTEM AND METHOD FOR AUTOMATIC TAKING OF FLUID SAMPLES

Technical Field

The present invention relates generally to automatic taking of fluid samples from a test object in the shape of a living being. More specifically, the invention relates to automatic taking of fluid samples having a composition representative of the composition of the fluid at the sample site of the living.

Background

In medical science and pharmaceutical industry there is often a need to perform pharmacokinetic studies on living beings, for example test objects in the shape of laboratory animals such as rats and pigs. In such studies, it is common to take a plurality of samples or specimens from the test object as well as injecting substances into the test object during the course of hours or days, in order to allow observation of gradual responses in the test object. In order to minimise time and cost consuming manual handling of taking specimen as well as the stress impact of such a manual handling on the laboratory animal, attempts have been made to automate the sample taking procedure.

In prior art there are automatic systems for taking of specimens from and for delivering injections to living beings, for example laboratory animals used for experimental purposes such as rats and pigs. A drawback with some of the prior art system is that the volume of a taken sample usually is much larger than the volume necessary for the analysis of a taken sample. The reason for withdrawing a much larger volume of the body fluid than the volume than is used for the analysis is to obtain a sample that is to be analysed that has a composition representative of the composition of the body fluid in the test object. Many systems of today utilises tubings comprising a rinsing fluid or the like and when a taken sample is introduced into the tubings it will be diluted due to the cross-mixing between the taken sample and the rinsing fluid. Consequently, the taken sample will not show a composition that is representative of the body fluid. Thus, if the taken sample is to be analysed, the analysis would not give a representative result.

The unnecessary large volume that has to be taken is especially a drawback when taking blood samples from test objects, e.g. rats and mice, having a small total blood volume. At taking of blood sample from rats or mice, it is only possible to take a blood volume that corresponds to approximately 1-2 weight-% of the animal without negatively

affecting the state of health of the living being. If larger sample volumes are taken, one has to interrupt the sample taking procedure for several days in order to let the test object recover before a new sample can be taken.

When using some of the systems available today, one has withdraw a blood volume of approximately 200 micro litres from the test object in order to obtain a taken sample having a low percentage of dilution. The system of today results in 10% dilution of a taken sample and in that only approximately 10 samples can be taken from a the test object, e.g. a rat, in order not to exceed the total volume of 2-3 millilitres that can be taken from the rat. Thus in repeated taking of blood samples it is desirable to minimise the total blood volume that is taken from the test object and that the entire or almost the entire volume of a taken sample is used for analysis. The latter is possible only if the taken blood sample has a low percentage of dilution.

In many pharmacological studies, it is also desirable to obtain more sample and samples having a smaller volume, which neither are possible with the automatic systems of today.

The prior art document US 4,691,580 to Fosslien shows a fluid sample apparatus wherein an air bubble is used to reduce cross-mixing of saline wash with blood samples and to separate blood samples.

The prior art document EP 0 389 719 to International Technidyne Corp shows an example of a sample collection and delivery system adapted for body fluid sample. The samples are transported in a lumen of a tubing from one end to other with a separation between each sample. A drawback with this system is that one or several samples (reference numeral 62 in EP 0 389 719) is taken prior to the sample (reference numeral 63 in EP 0 389 719) that is to be analysed in order to collect any residual of washing fluid that may remain in contact with the inner surface of the sample transfer tube. Thus, a larger volume of the sample is taken than is required for the analysis. This is especially critically when the samples are taken from a living being having a small total volume of the sample fluid. Thus fewer samples can be taken than if the volume required to be taken per analysed sample where less. Another drawback with the system is that the disclosed washing procedure (Fig. 2K in EP 0 389 719) causes all of the washing fluid flow to be directed through the catheter into the vessel of the living being. This supply of washing fluid to the vessel causes a dilution of the blood. If a new blood sample is taken its composition would not be the same as if the washing fluid was not supplied to the blood vessel. Thus in order to take samples having a representative composition, one has to wait

for a quit long time before taking another sample to be analysed. Another drawback with supplying washing fluid to the vessel is that it changes the fluid balance of the living being. Yet another drawback with supplying washing fluid to the vessel is that the washing fluid usually comprises heparin in order to prevent coagulation of blood in the catheter means but can be harmful to supply to the living being.

Object of the Invention

The overall object of the present invention is to solve the problem of taking a fluid sample of a body fluid having the same composition as the body fluid at the sample site of the test object. An aspect of the object is to provide an automatic system for taking a fluid sample from a test object that minimises the dilution of the taken sample.

A more specific object of the present invention is to provide a blood sample having a composition corresponding to the composition of blood in the normal blood flow at the sample site of a test object. An aspect of this object is to provide an automatic system for taking blood samples from a test object that minimises the dilution of the taken blood sample.

By means of the present invention, several advantages are achieved as compared to the prior art. Amongst others, a taken fluid sample having a higher concentration as compared to a fluid sample taken by a prior art system is achieved. Another advantage is that a minimal amount of rinsing solution is supplied to the sample site reducing the dilution of the body fluid as compared to the prior art systems. Yet another advantage is that it provides an improved procedure for washing the lumens of the catheter means, whereby a drug solution can be supplied to the sample site by means of the same catheter means that is used for taking the sample with a minimised risk of contamination.

Summary of the invention

The above-mentioned objects and aspects, amongst others, are obtained by the present invention. The invention refers to a system, a method, a set of disposables and a computer program product according to the independent claims. Preferred embodiments of the invention are specified in the dependent claims.

Brief description of the drawings

The present invention will be described in more detail with reference to the accompanying drawings, in which:

FIG. 1 schematically shows an embodiment of the inventive system;

FIGS. 2A – 2I schematically show parts of the embodiment of the inventive system of FIG. 1 and the steps of the sample taking procedure provided by the invention; and

FIG. 3 schematically shows an embodiment of a double lumen catheter means for use in the inventive system.

Detailed description of the invention

The present invention will now be described in more detail with reference to the accompanying drawings. FIG. 1 shows an embodiment of a system for automatic taking of specimens according to the invention. The figure schematically illustrates a control unit CU communicatively connected to pumping means P_A, P_B and a set of valves V. The control unit CU is configured to control the operation of the pumping means P_A, P_B and the set of valves V. The pumping means can for example be realised as a piston pump or a reciprocating pump. The system 10 according to the figure also comprises an analyser A communicatively connected to the control unit CU. However, it should be understood that the analyser can be a separate unit not comprised in the system 10 but instead connected to the system 10. The analyser A is configured to analyse a taken sample.

As shown in the FIGS. 2A-2I, the system 10 comprises also flexible tubings, e.g. first and second catheter means C_A and C_B, respectively. In the shown embodiment, the system 10 comprises further a plurality of valves V_{A1}, V_{A2}, V_{B1}, V_{B2}, V_{B3}, V_{B4} connected to the catheter means C_A, C_B and a first and second source of rinsing/washing fluid F_A and F_B, respectively. The first and second source of rinsing fluid F_A and F_B being arranged at valves V_{A1} and V_{B1}, respectively. It should be understood that the first and second rinsing fluid sources can be arranged as one single source having two outlet openings, each connectable to a valve in catheter means C_A and C_B, respectively.

The catheter means C_A and C_B comprises each a lumen. Further, several catheter parts or tubings can constitute the catheter means C_A and C_B. In the embodiment shown in FIGS. 2A-2I, the first catheter means C_A comprises a first part C_{A1} connecting the first pumping means P_A and a first valve V_{A1}, and a second part C_{A2} connecting the first fluid source F_A and the first valve V_{A1}. The catheter means C_A comprises further a third part C_{A3}

connecting the first valve V_{A1} and a second valve V_{A2}, and a fourth part C_{A4} connecting the second valve V_{A2} and a three-way junction C_J.

As also shown in FIG. 2A, the second catheter means C_B comprises a first part C_{B1} connecting the second pumping means P_B and a first valve V_{B1}, and a second part C_{B2} connecting the second fluid source F_B and the first valve V_{B1}. The catheter means C_B comprises further a third part C_{B3} connecting the first valve V_{B1} and a second valve V_{B2}, and a fourth part C_{B4} connecting the second valve V_{B2} and a third valve V_{B3}. A fifth part C_{B5} is arranged to connect the third valve V_{B3} and the three-way junction C_J, a sixth part C_{B6} connects the third valve V_{B3} and a fourth valve V_{B4}. A seventh part C_{B7} is arranged to connect the second and the fourth valves V_{B2} and V_{B4}, and an eighth part C_{B8} extends from the fourth valve V_{B4} to a sample tube T.

The valves are configured to control the flow path of the flow of a fluid in the catheter means and the pumping means are configured to control the flow rate and the flow direction of the fluid comprised in the catheter means.

It should be understood that the parts of the catheter means are only schematically illustrated in the FIGS. 2A-2I, e.g. are the dimensions, i.e. the diameter and the length, of the different parts not according to scale and serve only to exemplify principles of the invention.

The two-way arrows at each of the valves in FIG. 2A, indicate the possible flow directions provided by each of the plurality of valves comprised in the system, i.e. the possible flow paths of the fluid through the respective valve.

An embodiment of the inventive method for automatic taking of a specimen will now be described with reference to FIG. 2A – 2I.

In step 100 a rinsing fluid, e.g. a heparinised sodium chloride solution, has been supplied to i.a. the lumens of the tubings or catheter means C_A, C_B and possibly also to the pumping means P_A, P_B of the system 10, cf. FIG. 2A.

In step 102, an inlet V_I of the valve V_{A2} is opened and the pumping means P_A provides an suction action, whereby an amount of an immiscible fluid, e.g. an air bubble, AB is sucked into the lumen of the catheter means C_{A3}, cf. FIG. 2B. The flow direction and the operating direction of the first pumping means P_A is indicated by the arrows. The second pumping means P_B is not active.

In step 104, the air bubble AB is moved in the catheter means C_A towards the sample site SS, e.g. a blood vessel, of the test object. The movement of the air bubble AB and the rinsing solution in the catheter means C_A, C_B is accomplished by the pumping

means P_A, P_B. The control unit CU is configured to control the pumping means P_A, P_B to transport said immiscible fluid AB to the three-way junction C_J of the catheter means C_A, C_B. A first part AB_1 of said immiscible fluid AB will preferably be located the fifth catheter part C_{B5} of the second catheter means C_B and a second part AB_2 of said immiscible fluid AB will be located in the fourth catheter part C_{A4} of the first catheter means C_A. The first AB_1 and second AB_2 parts of the immiscible fluid AB is approximately of the same volume.

In order to accomplish the movement of the air bubble AB towards the three-way junction C_J, the control unit CU is preferably arranged to control the first pumping means P_A to provide a pushing action and the second pumping means P_B to provide a suction action. The pushing and suction actions being of the same size or almost of the same size. In other words the first and second pumping means P_A, P_B are preferably controlled to provide the same flow rate but in opposite directions. The arrows in FIG. 2C, indicate the flow direction of the rinsing fluid and the air bubble AB, and the operating directions of the pumping means P_A, P_B. FIG. 2C schematically shows the situation when the air bubble AB has been moved to the junction C_J.

An advantage will the present invention is that when the immiscible fluid is transported to the junction, the rinsing fluid comprised down streams of the immiscible fluid is transported to the junction and then via the second catheter means to a waste container or the like. Thus, no rinsing fluid is supplied to the sample site during this operation. Consequently, the body fluid at the sample site is not diluted.

In step 106, the first pumping means P_A is turned off and the flow path through the catheter means is maintained as before. The second pumping means P_B provides a pushing action, whereby causing the first part AB_1 of the air bubble AB to move towards the sample-taking end C_{TE} of the catheter means. The second pumping means P_B is turned off when the first part AB_1 of the air bubble AB reaches the sample-taking end C_{TE}.

The volume R of the rinsing fluid (cf. FIG. 2C) comprised in the sample-taking end C_{TE} of the catheter means C_A, C_B is small, approximately 5 micro litres, causing a minimal dilution of the body fluid when it is supplied to the body fluid.

As mentioned above, the control unit controls the operation of the pumping means. By means of the knowledge of the volume, i.e. the length and inner diameter, of the catheter means, and the flow rate caused by the pumping means, it is possible for the control unit to determine when a desired position is reached by a part of the fluid. Thus, it is possible to determine when to stop the operation of the pumping means in order to

accurately positioning the immiscible fluid at the junction. It is also possible to accurately positioning the first part of the immiscible fluid at the end opening of the sample-taking end. This is especially advantageously since the risk of introducing the first part of the immiscible fluid to the sample site is minimised. In the case the first part of the immiscible fluid is an air bubble, the risk of air embolism is eliminated.

FIG. 2D schematically shows the result of step 106 and the arrows indicates the flow direction of the rinsing fluid and the first part AB_1 of the air bubble and of the operating direction of the second pumping means P_B.

In step 108, a fluid sample is taken from the sample site SS. In the case of a blood sample, the desired sample volume is withdrawn from a blood vessel of the test object, by means of a suction action of the second pumping means P_B. In the catheter means, the first part AB_1 of the air bubble AB is located before the taken sample TS as indicated in FIG. 2E. During this operation, the first pumping means P_A is turned off. In some cases, it can be advantageously to withdraw a sample volume that is approximately five micro litres larger than the volume required for performing the analysis.

In step 110, the taken sample TS is transported towards the sample tube T by means of a suction action of the second pumping means P_B and a pushing action of the first pumping means P_A, cf. FIG. 2F. The taken sample TS and the rinsing fluid are separated by means of the first AB_1 and second AB_2 parts of the air bubble AB, respectively. This is accomplished by means of the first P_A and second P_B pumping means controlled to provided the same flow rate but in different directions, i.e. the second pumping means P_B provides a suction action and the first pumping means P_A provides a pressing action, or vice versa if the sample is to be moved in the opposite direction.

In step 112, the second pumping means P_B provides a pushing action, whereby the taken sample TS is transported in sixth C_{B6} and eighth C_{B8} parts of the second catheter means C_B towards a sample tube T arranged at a delivery end C_{DE} of the catheter means C_B. FIG. 2G.

In step 114, the taken sample TS is delivered to the sample tube T, by means of the pushing action of the second pumping means P_B. Cf. FIG. 2H.

In step 116, the lumens of the first and second catheter means C_A, C_B are rinsed/washed by providing a flow of rinsing solution through the catheter means C_A, C_B. The control unit CU control the first and second pumping means P_A and P_B to operate at the same rate, whereby the catheter means are rinsed without supplying rinsing fluid to the sample site SS via the sample-taking end C_{TE} of the catheter means. Cf. FIG. 2I.

If the first and second pumping means do not operate in a synchronised manner, i.e. if for example the pushing action of the first pumping means is smaller than the suction action of the second pumping means, an unnecessary volume of sample solution can be withdrawn from the sample site. On the other hand, if the pushing action of the first pumping means is larger than the suction of the second pumping means, rinsing fluid can be supplied to the sample site. This latter case can be desirable when the sample-taking end C_{TE} of the catheter means is to be rinsed. In such case, the flow of rinsing solution is preferably accomplished by means of the first pumping means P_A pushing with a slightly higher pressure than the second pumping means P_B is sucking. In this way the part of the catheter means C_{TE} attached to the sample site also can be rinsed, without supplying any rinsing fluid to the sample site of the test object. For example, the pumping means P_A can be pressing at 100% of a flow F and the pumping means P_B can be sucking at 90% of the flow F.

It should be understood that by controlling the pumping means P_A and P_B to operate at the same rate, the catheter means can be rinsed with out risking to supply rinsing fluid to the test object. This is especially an advantage when the test object is sensitive for supply of large volume of fluid. This is for example the case when the catheter means is connected to a blood vessel of a rat or a mouse, since the supply of rinsing fluid to the blood vessel would dilute the blood and thereby change the characteristics of the normal blood and the concentration of different components in the blood. Furthermore, the supply would also changed the fluid balance of the test object.

FIG. 3 schematically shows an embodiment of a double lumen catheter means C_A, C_B for using in the present invention. As shown, the catheter means comprises two lumen which at the junction coincidences to a single lumen. Further, at the end opposite to the sample-taking end, the catheter means C_A, C_B diverges into two separated catheter means C_A and C_B. Thus as described above, an aspirated air bubble can be moved from the valve inlet to the junction in the catheter part C_{A4} and the rinsing solution comprised in the catheter means in downs streams the air bubble will be transported in the catheter means C_{B5} towards the junction and then via the catheter means C_{B5} to a waste container. Thus, the rinsing fluid passes by the sample-taking end without being supplied to the sample site.

The present invention has been described with reference to an embodiment of the invention. However, it should be understood that several modifications and variations of the system and method of the invention could be accomplished without falling apart from the scope of the invention. The sources of rinsing fluid, F_A and F_B, can for example be

arranged as one single source of rinsing fluid. In the description text above, reference has been made to an air bubble, but it should be understood that another immiscible fluid, e.g. another gas or another suitable substance immiscible in the sample and the rinsing fluid could be used. In such cases, the immiscible fluid is for example contained in a container attached to the catheter means C_A at the valve V_{A2}.

The pumping means P_A and P_B can further be configured as two separated pumping means as described above but they can also be configured as one single double-acting suction and force pumping means with a first part having the capability of providing a pushing action and a second part having the capability of providing a suction action. The first and second part being configured to operate separately or at the same time. In cases having a double-acting pumping means, a third pumping means is arranged at the catheter means and configured to operate when the first and a second parts are operated separately and to compensate for the active first or second part. That is, to provide a suction action if one of the parts is providing a pushing action, and to provide a pushing action if one of the parts is providing a suction action.

Further, the invention can comprise a source of a drug solution connectable to said catheter means (C_A, C_B). Due to the inventive arrangement of the catheter means and the pumping means, a drug can be supplied to a test object via the catheter means by means of the pumping means and the catheter means can subsequently be thoroughly washed in order to remove any possible drug residuals before a sample is taken by means of the same catheter means and pumping means. Due to the advantageously way to provide a fluid flow through the catheter means, the catheter means can be thoroughly washed without supplying any rinsing fluid to the sample site.